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SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
SOUTH WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
HARLE, JENNIFER I	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,669	BRINGE ET AL.	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13,15-27,33 and 34* is/are pending in the application.

4a) Of the above claim(s) *1-11,14,28-32 and 35-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *12,13,15-27,33 and 34* is/are rejected.

7)☐ Claim(s) *26 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-55 are pending and were the subject of an Election/Restriction Requirement. Applicants elected Group III (Claim 15) without traverse and set forth the additional species if the search had to be broadened. Claims 12-13, 15-27, and 33-34 are pending. Claims 1-11, 14, 28-32, and 35-55 are directed to either non-elected invention or non-elected species.

Election/Restrictions

2. Applicant's election without traverse of Group III (Claim 15) in the reply filed on November 1, 2007 is acknowledged.

3. Claims 1-11, 14, 28-32, and 35-55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 1, 2007.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated that, "To fulfill the written description requirement, a patent

specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Goslelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its Claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. *In Regents of the University of California v. Eli Lilly & Co.* the court stated that, "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] Chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiefs, 984 F.2d at 1171,25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinati0ns other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is

"not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure, presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not: constitute a representative number of species to adequately describe a broad generic. In *Goslelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Goslelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M PEP § 2163. While all of the factors have been considered, a sufficient amount for a prima facie case are discussed below.

(1) The nature of the invention and (2) The breadth of the claims

In the instant case, the claims are drawn to a composition for treating or preventing hypercholesterolemia comprising beta-conglycinin, or fragments thereof and an oil body associated

protein, wherein the beta-conglycinin and the oilbody associated protein are present in an amount effective to provide a synergistic effect for the treatment or prevention of hypercholesterolemia. The claims are very broad because they refer to any fragment (2 or more amino acids) of beta-conglycinin, which has 3 different sub-units. They literally read upon millions and millions of compounds.

(3) Level of skill and knowledge in the art and (4) Predictability or unpredictability in the art

It is known in the art that beta-conglycinin (7S or 7S globulin) lowers cholesterol, activates low-density lipoprotein (LDL) receptors, lowers LDL cholesterolemia, i.e. it would treat hypercholesterolemia by lowering cholesterol levels and LDL levels. See, e.g., Manzoni, et al., Soybean protein products as regulators of liver low-density lipoprotein receptors. II. alph-alpha' deficient mutant differently affect low-density lipoprotein receptor activation, Journal of Agricultural and Food Chemistry, July 1998, Vol. 46, No. 7, pp. 2481-2484. It is also known in the art that the alpha' subunit of beta conglycinin affects cholesterol, while the beta subunit has no impact on cholesterol levels. A subunit is a fragment of beta-conglycinin. It is further known in the art that 7S globuin (beta-conglycinin) reduces neutral fat, i.e. blood cholesterol, and that effect is enhanced when oil-body proteins and phytates are removed, where such an effect was demonstrated in animal models. Kohno, et al. (US 2004/0014640), Abstract, cols. 1-4, Example 1, Comparative Example 1. Kohno further discloses that a reduction in dosing occurs when you remove both the phytate and oil-body proteins. Kohno, et al., col. 2. Moreover, it is known in the art that synergy is a confusing topic and is profusely littered with technical terms that are not always clearly defined. M.C. Berenbaum, Synergy, additivism and antagonism in immunosuppression, A critical review, Clin. Exp. Immunol, 1977, Vol. 28, pp. 1-18 (Berenbaum1) and M.C. Berenbaum, What is

Synergy?, Pharmacological Reviews, 1989, Vol. 1969, Vol. 41, pp. 93-141 (Berenbaum2). Berenbaum teaches that the basic difficulty is that most investigators use fallacious criteria for determining the nature of drug interactions – the compare the effect of the agents used in combination with the sum of their effects when used alone. Berenbaum1, pg. 1 and Berenbaum2, 95. However , while this comparison is experimentally straight-forward, it is based on assumptions that are wrong, it leads to endless confusion, and conclusions based on it are generally valueless. Berenbaum1, pg. 1 and Berenbaum2, 95. Berenbaum states that the correct method for analyzing drug interactions is, in most cases, more laborious and involved, but conclusions upon which it is based are reliable. Berenbaum1, pg. 1 and Berenbaum2, 95-96. Berenbaum describes synergy as a combination of agents that is more effective than is expected from the effectiveness of its constituents and one less effective describes antagonism and thus synergy and antagonism imply that the different constituents affect each other's actions, i.e. they interact pharmacologically; additivism implies that they do not. Berenbaum1, pp. 1-2 and Berenbaum2, 95 and 98. Berenbaum sets forth the problems with current methods of determining synergy and sets forth a method of determining synergy that overcomes these problems for both homoergic and heterergic combinations. Berenbaum1, pp. 2-8 and Berenbaum2, 95-131. Berenbaum then describes the minimum requirements for demonstrating synergy, additivism or antagonism. Berenbaum1, pp. 8-12 and Berenbaum2, 100-116. Berenbaum then describes the clinical implications of searching for synergy and the advantages that can result, such as cost and potential shortage of drugs. Berenbaum1, pp. 16-17 and Berenbaum2, 100-116 and 125-130. Thus Kohno provides a teaching away from 7S globulin with oil-body proteins providing synergy.

With regards to preventing hypercholesterolemia, the art is silent. Hypercholesterolemia may be influenced by a variety of factors, such as diet, genetics, amount of exercise, other disease states contributing to the disease, for example diabetes. The ability to prevent, i.e. to keep from happening requires that one knows all the risk factors and the ability to predict which members of the populace will get the disease. As there is sometimes a genetic component and there is no current screening for the gene(s), this populace can not be elucidated before the individual has high cholesterol. Prevention becomes unpredictable. With regards to synergy, it is not predictable because one must test the compounds in order to know if there is synergy and the sheer number of fragments creates an exponential issue.

(5) The relative skill of those in the art

Taking into account the quantity of information available and the known methodologies, the level of skill in the art is low.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples

The specification provides eight different sequence fragments of beta-conglycinin and provides guidance as to what the high molecular weight fraction of soy proteins. We know from the art that two subunits provide cholesterol lowering effects. The specification provides enriching crude plant proteins with an isolated oil-body protein 1, 10, 100, 200, 1000 or more times or 1, 5, 10, 50, 100 or more fold relative to a purified fraction such as HMF. Pg. 14. The specification further provides that oil body associated proteins are added to a final concentration of about 0.5%, 1%, 3%, 5%, 10%, 20% or more by weight including all intermediate ranges within these concentrations. The specification discusses isolating mammalian lipoproteins but not any

particular one. Pg. 20. However, the specification does discuss egg yolk lipoproteins, separately. Pp. 20-21. The specification discloses typical formulations of an isolated soy material and an isolated oil body associated protein in the presence or absence of at least one additive compound may be combined to form a composition of the invention, such as soy flour with mammalian lipoprotein (with and without at least one additive compound, soy milk powder with mammalian lipoprotein (with or without at least one additive compound), soy protein concentrate with mammalian lipoprotein (with or without at least one additive ingredient), soy protein isolate with mammalian lipoprotein (with or without at least one additive ingredient), high molecular weight fraction with mammalian lipoprotein (with or without at least one additive ingredient), isolated soy polypeptide with mammalian lipoprotein (with or without at least one additive ingredient), glycinin or a subunit thereof with mammalian lipoprotein (with or without at least one additive ingredient), beta-conglycinin or a subunit thereof with mammalian lipoprotein (with or without at least one additive ingredient), at least one of SEQ ID Nos; 2, 3, 4, 5, or 6 with mammalian lipoproteins (with or without at least one additional ingredient). Pp. 22-29. However, of all these compositions, only 14 or 7 (if you only look at the isolated soy material for characterization of the isolated soy material), exemplify beta-conglycinin and mammalian lipoproteins. It is worth noting that a vast plethora of these compositions were not tested for lowering cholesterol and neither synergy nor prevention was ever shown. Additionally because the compositions only refer to mammalian lipoproteins, one does not know if one or many mammalian lipoproteins were used. Nor does one know which mammalian lipoprotein(s) were used. As set forth in the specification, generally speaking, most eukaryotic cells from species such s plants mammals, non-mammalian cells, algae and yeast contain intracellular lipid particles with associated proteins embedded. Pg. 18. Each

mammal would have it own lipoproteins, which like the oleosins would differ from species to species. Thus, there is at least one protein and probably more associated with each species. The examples include making the fragment high molecular fraction, trypsinization fragments (but no sequences set forth so we don't know if there is overlap with the eight SEQ ID Nos provided). Isolating the components of the high molecular weight fraction to include the alpha, alpha' and beta subunit of beta-conglycinin, where many peptides were produced with trypsinization. Example 1. The effect of HMF on cholesterol uptake was set forth in Example 2. HMF was tested alone and not in conjunction with any oil-body protein. Thus the only guidance provided by the Applicant is that you combine mammalian lipoproteins with various isolated soy proteins with wide ranges of oil-body associated proteins for inclusion. No specific guidance is provided with respect to mammalian lipoproteins. No specific mammalian lipoproteins are provided, with the exception of egg yolk lipoprotein and that is separated from mammalian lipoproteins. No specific guidance is provided with respect to the cholesterol lowering properties of individual fragments, just sets forth eight sequences, trypsinization. No specific guidance is provided for creating synergistic amounts. Synergy is only mentioned in the specification as it relates to being present. No specific guidance as to amounts, which particular proteins exhibit synergy. No examples are provided of any synergistic compounds. No specific guidance if provided with respect to the fragments of beta-conglycinin. Eight potential fragments and the subunits are disclosed but their relationship to each other and their use for cholesterol lowering has not been determined. Thus, the specification does not provide any examples of formulations displaying synergy, cholesterol lowering or hypercholesterolemia treatment/prevention or fragments.

(8) The quantity of experimentation necessary

Considering the state of the art as discussed by the references above, the unpredictability of synergy and prevention of hypercholesterolemia and the lack of guidance provided in the specification with regards to proportions providing synergy, the cholesterol lowering effect of the fragments, the lack of a consensus sequence or necessary amino acids in the fragments, one of ordinary skill in the art would be burdened with undue experimentation to determine synergistic formulations, effective fragments, particular mammalian lipoproteins that lower cholesterol, and prevention. One would even have to show that synergy exists for these formulations, including the millions of fragments of beta-conglycinin with all of the different oil-body proteins., including all of the different plant specific oil body proteins – the amino acid compositions are not identical, lipoproteins – including mammalian lipoproteins (again a variety in a species and they are not identical from species to species), egg yolk lipoprotein or fat globule membrane protein.

Claim Objections

6. Claims 26-27 (and would have included 28-30 if they were not withdrawn as being to non-elected species) objected to because of the following informalities: the dependence of the claims appears to be incorrect, as they are dependent upon claim 20, which claims a further added compound and these are not further added compounds but should be dependent off of claims 12 or 15 because that is where oil body associated proteins are claimed of which lipoprotein is one. Appropriate correction is required.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 12, 15-19, 26-27 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno, et al., WO 02/26243 A1 (Kohno, et al. EP 1 323 425 A1 - English Equivalent) in view of Yamada, et al, Increased clearance of plasma cholesterol after injection of apolipoprotein E into Watanabe heritable hyperlipidemic rabbits, Proc. Natl. Acad. Sci. USA, January 1989, Vol. 86, pp. 665-669 and further in view of M.C. Berenbaum, Synergy, additivism and antagonism in immunosuppression, A critical review, Clin. Exp. Immunol, 1977, Vol. 28, pp. 1-18 (Berenbaum1) and M.C. Berenbaum, What is Synergy?, Pharmacological Reviews, 1989, Vol. 1969, Vol. 41, pp. 93-141 (Berenbaum2).

Kohno discloses that 7S globulin (beta-conglycinin) and 11S globulin (glycinin) were found to be excellent in terms of an ability of reducing blood cholesterol or neutral fat in blood and liver as compared to casein, which is an animal protein. [0003] and [0013]. Kohno also discloses that the 7S globulin and the phytate reduced 7S globulin exhibited more excellent blood neutral fat reducing abilities, as compared to the control, casein, with phytate reduced 7S globulins exhibiting an especially high neutral fat reducing effect, including cholesterol and in response to the onset of this neutral fat reducing effect, the blood cholesterol is reduced. Table 4, pg. 6, Table 7, page 7, Table 8, page 8. Kohno additionally discloses that by further removing a membrane protein rich oil-body-associated protein, which contaminates a soybean protein the efficacy of the 7S globulin as an active ingredient is enhanced, which is the main ingredient of this invention. [0012], [0014], [0015], [0017] and Production Example 2, pg. 5, lines 7-25. Kohno further discloses that a composition of the invention can be formulated as an oral composition whose active ingredient is a fraction obtained (7S globulin, 7S globulin without oil body associated protein of soybean, 7S

globulin phytate reduced, and 7S globulin phytate reduced without oil body associated protein of soybean) or a soybean protein, and formulated into various dosage forms such as powders, sugar-coated tablets and granules by known methods optionally together with other excipients and additives or incorporated into a food, as the active ingredient. [0018], [0019],[0041], Claims 1-4. Noting that the 7S globulin reduced total cholesterol more than 7S-PH, however, 7S-PH had a higher HDLC which is more desirable. [0038]-[0039], Table 9, Table 10, [0040] However, Kohno does not disclose any mammalian lipoprotein or its use for lowering cholesterol or the possibility of synergy.

Yamada discloses apolipoprotein E (apoE) plays an important role in lipoprotein by lowering cholesterol. Abstract. Yamada also discloses that LDL cholesterol is mainly removed from blood plasma by hepatic LDL receptors that interact with two specific ligands on lipoproteins, apolipoprotein B-100 (apoB-100) and apoE, and that lipoproteins rich in apoE, such as large very low density lipoprotein (VLDL) and beta-VLDL, have a much higher affinity for LDL receptors than LDL, which contains only apoB-100. Pg. 665. Additionally, Yamada disclosesthat recent research has demonstrated two lipoprotein subclasses containing apoB-100:B,E particles containing apoE and -B and B particles lacking apoE. Pg. 665. Yamada further discloses that the presence of apoE has been shown to have a profound influence on the removal of apoB-100 in VLDL particles from the blood of normal rabbits and their conversion to lipoproteins of higher density [intermediate density lioprotein (IDL) and LDL and that in WHHL rabbits, the rate of removal of VLDL-B,E particles from the blood was 4 fold higher than that of VLDL-B particles suggesting that in WHHL rabbits a small number of LDL receptors expressed on the surface of hepatocytes or chylomicron-remnant receptors participate in the removal of lipoproteins containing several molecules of apoE

by interacting with apoE. Yamada discloses that the WHHL rabbit is an excellent animal to test the effect of agents that could alter the interaction of lipoproteins with lipoprotein receptors and in the current study massive amounts of apoE were injected into WHHL rabbits to enrich lipoproteins in the receptor-active protein apoE supporting the hypothesis that such lipoproteins would be removed much more efficiently through either the chylomicron-remnant receptor or the mutant LDL receptor resulting in the decreased level of plasma cholesterol. Pp. 665-667. Yamada discloses that plasma cholesterol is lowered by 20% mainly in VLDL and KDL between 4 and 8 hours after injection, while later LDL cholesterol fell substantially and lowered plasma cholesterol levels were maintained up to 24 hours after injection. Pp. 667-668. Moreover, Yamada discloses that the rate of removal of VLDL incubated with apoE (VLDL-E) was 3-fold higher than that of VLDL, whereas there was no difference between I +LKL-E and I+LDL suggesting that the number of apoE molecules on VLDL particles is critical for VLDL clearance. Pg. 669. Yamada further discloses that while apoE lowers cholesterol, more studies using biosynthetic apoE are needed to determine whether it will reduce the rate of atherogenesis in WHHL rabbits and the mechanism by which cholesterol is lowered after leaving the blood, i.e. excreted as bile acids, secreted as VLDL, or incorporated into foam cells. Pg. 669. However, Yamada does not disclose any possibility of synergy.

Synergy is a confusing topic and the art is profusely littered with technical terms that are not always clearly defined. Berenbaum teaches that synergy is a confusing topic, whose art is profusely littered with technical terms that are not always clearly defined and the basic difficulty is that most investigators use fallacious criteria for determining the nature of drug interactions – the compare the effect of the agents used in combination with the sum of their effects when used alone.

Berenbaum1, pg. 1 and Berenbaum2, 95 and 98. However, while this comparison is experimentally straight-forward, it is based on assumptions that are wrong, it leads to endless confusion, and conclusions based on it are generally valueless. Berenbaum1, pg. 1 and Berenbaum2, 95. Berenbaum states that the correct method for analyzing drug interactions is, in most cases, more laborious and involved, but conclusions upon which it is based are reliable. Berenbaum1, pg. 1 and Berenbaum2, 95-96. Berenbaum describes synergy as a combination of agents that is more effective than is expected from the effectiveness of its constituents and one less effective describes antagonism and thus synergy and antagonism imply that the different constituents affect each other's actions, i.e. they interact pharmacologically; additivism implies that they do not. Berenbaum1, pp. 1-2 and Berenbaum2, 95 and 98. Berenbaum sets forth the problems with current methods of determining synergy and sets forth a method of determining synergy that overcomes these problems for both homoergic and heterergic combinations. Berenbaum1, pp. 2-8 and Berenbaum2, 95-131. Berenbaum then describes the minimum requirements for demonstrating synergy, additivism or antagonism. Berenbaum1, pp. 8-12 and Berenbaum2, 100-116. Berenbaum then describes the clinical implications of searching for synergy and the advantages that can result, such as cost and potential shortage of drugs. Berenbaum1, pp. 16-17 and Berenbaum2, 100-116 and 125-130.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have combined 7S globulin (beta-conglycinin) with the mammalian lipoprotein apoE because it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose as the idea of combining them flows logically from their having been individually taught in

the prior art. See MPEP 2144.06, In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). It would have been obvious to one of ordinary skill in the art at the time of the invention to have sought synergistic combinations because of the potential advantages taught by Berenbaum, i.e. cost, lower overall amounts of the drugs used, and less lack of potential shortage. It would have been obvious to one of ordinary skill in the art at the time of the invention to have determined the appropriate amounts 1%-5%, 5%-10%, greater than 10%, about 30% to about 50% of an oil body associated protein or greater than 40% of beta-conglycinin, based upon well known factors in the art such as height and weight, amount of cholesterol to be lowered, severity of the disease and the synergistic amounts.

9. Claims 12-13, 15, 20, 24, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno, et al., WO 02/26243 A1 (Kohno, et al. EP 1 323 425 A1 - English Equivalent) in view of Yamada, et al, Increased clearance of plasma cholesterol after injection of apolipoprotein E into Watanabe heritable hyperlipidemic rabbits, Proc. Natl. Acad. Sci. USA, January 1989, Vol. 86, pp. 665-669 and further in view of M.C. Berenbaum, Synergy, additivism and antagonism in immunosuppression, A critical review, Clin. Exp. Immunol, 1977, Vol. 28, pp. 1-18 (Berenbaum1) and M.C. Berenbaum, What is Synergy?, Pharmacological Reviews, 1989, Vol. 1969, Vol. 41, pp. 93-141 (Berenbaum2) and further in view of Hori, et al., Soy Protein Hydrolyzate with Bound Phospholipids Reduces Serum Cholesterol Levels in Hypercholesterolemic Adult Male Volunteers, Boisci. Biotechnol. Biochem., 2001, 65(1), pp. 72-78.

Kohno, Yamada and Berenbaum(1 and 2) disclose as set forth above. However, none of them disclose that the beta-conglycinin (7S globulin) could be at least partially hydrolyzed. Hori discloses that after 3 months of testing in adult males, whose total serum cholesterol were above

220 mg/dl, serum total cholesterol (hypercholesterolemic subjects) decreased significantly from the initial level (15%, $p<0.01$) and (27.4%, $p<0.01$), the LDL level also decreased significantly (27.7%) and (43.6%), the LDL/HDL ratio also decreased significantly (47.4%, $p<0.01$) and (64.0%, $p<0.01$), and the HDL increased (40.1%) and (61.1%) by administration of 3 grams or 6 grams per day of c-SPHP. Abstract, pp. 74-76, Fig. 2, and Table 2. Hori additionally discloses that soy protein and the high molecular weight fraction obtained from the hydrolyzate of soy protein are known for their ability to reduce serum cholesterol levels in humans and in experimental animals, possibly via inhibition of cholesterol absorption in the intestine and a cholesterol-lowering effect of purified phopholipids has also been reported. Pg. 72. Hori also discloses that the binding of phopholipid to soy protein hydrolyzate in large quantities brings stronger cholesterol –lowering effects. Pp. 72-76, Fig. 2 and Table 2. Hori further discloses that lecithinated textured vegetable protein (containing 6% lecithin approximately 90 grams), reduced serum total cholesterol and increased HDL-cholesterol with type-II hyperlipidemic patients and that HMF (approximately 20 grams), the high molecular weight fraction, obtained from the hydrolyzate of soy protein, reduces total cholesterol levels of midlly hypercholesterolemic subjects more effectively than intact soy protein. Pg. 76.

Thus it would have been obvious to substitute HMF or c-SPHP for betaconglycinin, synergistic beta-conglycinin and apolipoprotein E, because HMF or c-SPHP lowered cholesterol better than intact soy protein. See also MPEP 2144.06 and In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). It would have been obvious to have added another cholesterol lowering composition, the lecithin phospholipid discussed above to the synergistic beta-conglycinin and apolipoprotein E of Kohno, Yamada and Berenbaum(1 and 2) because the addition of another ingredient with the same cholesterol lowering property is prima facie obvious because

the idea of combining them flows logically from their having been individually taught in the prior art. See also MPEP 2144.06 and In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

10. Claims 12, 15, 26-27 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno, et al., WO 02/26243 A1 (Kohno, et al. EP 1 323 425 A1 - English Equivalent) in view of Yamada, et al, Increased clearance of plasma cholesterol after injection of apolipoprotein E into Watanabe heritable hyperlipidemic rabbits, Proc. Natl. Acad. Sci. USA, January 1989, Vol. 86, pp. 665-669 and further in view of M.C. Berenbaum, Synergy, additivism and antagonism in immunosuppression, A critical review, Clin. Exp. Immunol, 1977, Vol. 28, pp. 1-18 (Berenbaum1) and M.C. Berenbaum, What is Synergy?, Pharmacological Reviews, 1989, Vol. 1969, Vol. 41, pp. 93-141 (Berenbaum2) and further in view of Lovati, et al. and Manzoni, et al., Soybean Protein Products as Regulators of Liver Low-Density Lipoprotein Receptors. I. Identification of Active Beta-Conglycinin Subunits II. Alpha and Alpha' Rich Commercial Soy Concentrate and Alpha' Deficient Mutant Differently Affect Low-Density Lipoprotein Activation, J. Agric. Food Chem., 1998, Vol. 46, pp. 2474-2484.

Kohno, Yamada, and Berenbaum(1 and 2) disclose as set forth above. However none of them disclose that the alpha' subunit lowers cholesterol.

Lovati discloses the ability of the different soy globulins to upregulate low-density lipoprotein (LDL)and metabolism in human heptatoma cells (Hep G2) in an attempt to identify peptide components responsible for the upregulation of the LDL receptor by in parallel, the metabolism of soy globulins, added to the culture medium, was investigated by two-dimensional electrophoresis and immunodetection, resulting in no marked changes in the cell protein pattern

after addition of the soy globulins with electrophoresis and intact 7S components, alpha and alpha' subunits were not detectable inside the cells while the beta subunit was detected inside cells by immunodetection. Abstract. Lovati additionally discloses that the reduction of cholesterolemia is apparently associated with an activation of the receptor-mediated catabolism of the major cholesterol carriers in plasma, low-density lipoproteins (LDL). Pg. 2472. Lovati discloses that evidence from the laboratory suggests that human heptatoma cells (Hep G2) show an increased expression of LDL receptors, when incubated in the presence of isolated soy globulins (beta-conglycinin, 7S globulin, and glycinin, 11S globulin) with beta-conglycinin being markedly more effective vs glycinin in the LDL receptor upregulation, being also recognized by a specific uptake and degradation system. Lovati demonstrated that the alpha and alpha' subunits were able to increase LDL receptor activity sharply, both when determined as LDL uptake and, somewhat less, as LDL degredation, while the isolated beta subunit does not show any upregulating property. Pg. 2477. Lovati additionally discloses that preliminary data from the laboratory had indicated that the isolated 7S soy globulin can actively increase uptake and degradation of the LDL from human serum in liver cell systems, suggesting a mechanism that might well be responsible for the plasma cholesterol reduction in man, where the prior evidence in patients indicates that LDL receptor expression on circulating cells (Lymphocytes, where it parallels that found in hepatocytes) increases after the consumption of soy protein. Pp. 2477-78. Lovati teaches that the overall protein makeup on Hep G2 cells, a well established human cell line, exposed to the alpha+alpha' and beta-subunits, only the alpha+alpha' subunits in their native forms completely disappeared after cell exposure, whereas most of the beta-subunits were unaffected or barely reduced in size and furthermore, only intact chains were observed in the culture medium; i.e., no proteolysis fragments seemedto lost from

cells and to accumulate in the medium. Pg. 2478. Lovati additionally teaches that when the protein material bound at the cell surface was released by heparin treatment and adequately concentrated, immunological identification allowed them to conclude that the whole 7S soy globulin preferentially interacts with heparin-sensitive binding sites, with little competition from the more abundant protein supplied by the incubation medium. Pg. 2478. Lovati also discloses that the selected laboratory method provides an adequate indicator as to the identify of elements responsible for the biological effects, i.e. the identity of the factor(s) in soy diet responsible for the plasma cholesterol reducing properties are the alpha+alpha'. Pp. Abstract, 2476-2479. Manzoni discloses activation of the low-density lipoprotein (LDL) receptors has been described in a human hepatoma cell line (Hep G2), which as an in vitro model supports a direct activity of soy protein component(s) in lowering LDL cholesterolemia. Manzoni additionally discloses that the reduction of cholesterolemia induced by dietary soy proteins is believed to be associated with an activation of liver LDL receptors in man and experimental animals, where laboratory studies have indicated that beta-conglycinin from soy appears to be the component responsible for LDL receptor activation and that when Hep G2 is presented with 7S globulins, the alpha + alpha' subunits are extensively degraded and, in parallel, LDL receptor activity is markedly stimulated, resulting in a hypocholesterolemic response, while in contrast the beta subunits go largely undigested, as much as they seem unable to activate the LDL receptors, no reduction of cholesterolemia. Pg. 2481. Manzoni teaches a commercial isoflavone-poor, heat-hydrolyzed soy preparation found effective in human hypercholesterolemia (Croksoy), which was shown by clinical experience to significantly reduce cholesterolemia in man, and a mutant soy cultivar, devoid of the alpha' subunit (Keburi) were tested in the in vitro model, while Croksoy proved to have a similar activity as the whole 7S

globulin the alpha' free Keburi variant showed no effect on LDL receptor, no reduction of cholesterolemia. Abstract, pg. 2481. Manzoni tested proteins from Croksoy and the 7S globulin from the Keburi soy variety were examined by two-dimensional electrophoresis and in the case of Croksoy, staining for protein and glycoproteins as well as immunostaining for 7S related components was carried out with the results that the 7S from the Keburi variety is completely devoid of the alpha' subunit and the Croksoy contains the major soy globulins degraded by industrial processing with the result that the predominance of peptides are in the Mr range around 30,0000; a large percentage of the material, as shown by immunodetection and sugar staining, may be identified as 7S derived peptides. Pg. 2482. To confirm or dismiss the hypothesis that the presence of 7S globulin (or its degradation products) and, particularly, of its alpha subunits is crucial in eliciting LDL receptor activation, the two soy preparations were confronted with cultured Hep G2 cells and their activity was compared to that of a 7S globulin isolated from standard soybean flour with the results, listed in Table 1, confirm the dose-dependent activity of the 7S globulin and moreover, an almost equivalent activity (on a weight basis) of the Croksoy preparation, rich in 7S degradation products, versus controls noting that a 73% increase in LDL uptake and degradation is detected following preincubation with the highest concentration of Croksoy, while in contrast non LDL receptor activation is observed in the presence of 7S from the Keburi variant. Pg.2482. Manzoni teaches that Croksoy is routinely used by our group in the dietary treatment of hypercholesterolemic type IIa patients and has been shown to modify serum and LDL cholesterol concentrations according to base-line cholesterolemia, from a minimum of -3.3% in subjects with cholesterol in the borderline range, way up to -19.6 (LDL cholesterol -24%) in clear cut hypercholesterolemics. Pg. 2483. Manzoni additionally teaches that Keburi, a mutant

soybean variety lacking the alpha' subunit of beta conglycinin, offered an unique possibility to test which of the alpha + alpha' components in 7S globulin is responsible for the upregulation of the LDL receptor activity, reduction of cholesterolemia, noting the very clear lack of activity of this mutant storage protein on LDL receptor activation at either of the concentrations. Pg. 2483. Manzoni concludes that the LDL receptor activating cholesterol-lowering properties of soy protein may reside in some specific amino acid stretches of 20-30 amino acids, i.e. either those present in the consensus sequence drawn among all 7S globulins characterized thus far, but not in the beta-subunit, or in the 37 amino acid stretch occurring at the NH2 terminal of alpha' and not of the alpha subunit, noting that such peptides are being synthesized by solid-phase methodology and will be tested in the above-described system and these if found active could be could eventually be introduced into the alpha/alpha' subunit in the soybean genome by site-directed mutagenesis. It would have been obvious to one of ordinary skill in the art at the time of the invention was made to choose from a finite number of consensus sequences or the 37 amino acid stretch occurring at the NH2 terminal of alpha' with a reasonable expectation of success for the 37 amino acid stretch because we already know that a plant devoid of alpha' does not activate the LDL receptors, produces no reduction in cholesterolemia and thus confirming the alpha' subunit for reducing cholesterolemia. It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have utilized the alpha' subunit with the synergistic combination of beta-conglycin (replaced by the alpha' subunit) and apoE because we already know that it reduces cholesterolemia from the in vitro data above (Croksoy contained alpha and alpha' subunits while Keburi contained only the alpha subunit and beta subunit).

11. Claims 12, 15, 20-22, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno, et al., WO 02/26243 A1 (Kohno, et al. EP 1 323 425 A1 - English Equivalent) in view of Yamada, et al, Increased clearance of plasma cholesterol after injection of apolipoprotein E into Watanabe heritable hyperlipidemic rabbits, Proc. Natl. Acad. Sci. USA, January 1989, Vol. 86, pp. 665-669 and further in view of M.C. Berenbaum, Synergy, additivism and antagonism in immunosuppression, A critical review, Clin. Exp. Immunol, 1977, Vol. 28, pp. 1-18 (Berenbaum1) and M.C. Berenbaum, What is Synergy?, Pharmacological Reviews, 1989, Vol. 1969, Vol. 41, pp. 93-141 (Berenbaum2) and further in view of Yaguang Liu (US 5, 968,516).

Kohno, Yamada and Berenbaum(1 and 2) disclose as set forth above. However, none of them teach the additional ingredient of soybean saponins, particularly the isoflavone genistein.

Liu discloses that soybean saponins[1] can treat cardiovascular disease, increase the immune function and decrease serum lipids, where the dosage is about 20 mg per day where it can be used as a drug, health food or food additives which can be added into other food. Col. 1, lines 36-64. Liu also discloses that the invention relates to a new extracting method of producing soybean's saponins from soybean residue which is a by product after extracting oil resulting in great economic, environmental value, saving of a lot of organic solvents, cheaply. Col. 2, lines 16-37. Liu additionally teaches that soybean saponins can significantly decrease cholesterol, triglycerides and free fatty acids. Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to have added the soy bean saponins of Liu to the synergistic beta-conglycinin and apoE of Kohno, Yamada and Berenbaum(1 and2) because it is prima facie obvious as the idea of

[1] Soybean saponins would have implicitly contained the isoflavone, genistein because it is a soybean saponin and none are separated out.

combining them flows logically from their having been individually taught in the prior art. See also, MPEP 2144.06 and In re Kerkhoven, cited above.

12. Claims 12, 15, 20-22, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno, et al., WO 02/26243 A1 (Kohno, et al. EP 1 323 425 A1 - English Equivalent) in view of Yamada, et al, Increased clearance of plasma cholesterol after injection of apolipoprotein E into Watanabe heritable hyperlipidemic rabbits, Proc. Natl. Acad. Sci. USA, January 1989, Vol. 86, pp. 665-669 and further in view of M.C. Berenbaum, Synergy, additivism and antagonism in immunosuppression, A critical review, Clin. Exp. Immunol, 1977, Vol. 28, pp. 1-18 (Berenbaum1) and M.C. Berenbaum, What is Synergy?, Pharmacological Reviews, 1989, Vol. 1969, Vol. 41, pp. 93-141 (Berenbaum2) and further in view of Graham Edmund Kelly (US 5,830,887).

Kohno, Yamada and Berenbaum(1 and 2) disclose as set forth above. However, none of them teach the additional ingredient of soybean saponins, subgroup phytoestrogens, subsubgroup isoflavones, particularly the isoflavone daidzein.

Kelly discloses compositions enriched with natural phyto-oestrogens, or isoflavones, particularly genistein, daidzein, formononetin and biochanin A, or their natural glycoside form, or their analogs; and preferrablegenistein and/or its' methylated derivative biochanin A to daidzein and/or its methylated derivative formononetin is between 1:2 to 2:1; that are useful for treating hypercholesterolemia, i.e. lowering cholesterol, including LDL and VLDL. Abstract, col. 5, lines 53-66, col. 6, lines 15-18, col. 6, lines 29-56, cols. 10-11, lines 57-19, claims 1, 3-9, and 11-13. Kelly provides a good overview of 4 Types of Phyto-oestrogens, including isoflavones. Cols. 1-2, lines 26-28. Kelley discusses the difference in diets between the East and the West and provides a strong rationale for phyto-oestrogens and isoflavones, particularly genistein and daidzein, lowering

cholesterol. Cols. 3-5. Kelley also discloses that the supplement containing the isoflavones contains an excipient, a diluent, a carrier or the like or else the supplement is mixed with food or can be consumed directly, i.e. formulations may be a variety of kinds, such as nutritional supplement, pharmaceutical preparations, vitamin supplements, food additives or foods supplemented with the specified phyto-oestrogens of the invention, liquid or solid preparations, including drinks, sterile injectable solutions, tablets, capsules, powders, drops, suspensions, or syrups, ointments, lotions, creams, pastes, gels or the like. Col. 5, lines 58-60, col. 9, lines 48-61. Kelly additionally discloses that in vitro and in vivo studies have indicated that genistein, biochanin A, equol, daidzein formonnetin all have oestrogenic activity in descending order and that treating hypercholesterolemia, i.e. lowering cholesterol is performed by a phyto-oestrogen function of modulating the production and/or function of endogenous sex hormones in humans to modify or produce health improving effects, also included are treatment of PMS, which includes pre-menstral tension (PMT), and menopausal symptoms; reduced risk of developing cancer of the prostate; reduced risk of cancer of the breast; reduced risk of development of cancer of the uterus; reduced risk of development of cancer of the large bowel; reduced risk of development of many untoward symptoms (including dry vagina, peripheral flushing, depression, etc.) commonly associated in women with menopause; and for treating benign breast disease in women (benign or cystic breawst disease associated with non-malignant swelling and tenderness of breast tissue). Cols. 10-12, lines 57-16. Kelly further discloses experimental results where the total cholesterol was lowered when taking isoflavones or daidzein and genistein. Examples 3 and 4 - cols 13-14, lines 15-19.

Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to have added the preferred isoflavone combination of daidzein and genistein of Kelly to

the synergistic beta-conglycinin and apoE of Kohno, Yamada and Berenbaum(1 and2) because it is prima facie obvious as the idea of combining them flows logically from their having been individually taught in the prior art. See also, MPEP 2144.06 and In re Kerkhoven, cited above. Moreover it would have been obvious to one of ordinary skill in the art at the time of the invention to have added the preferred isoflavone combination of daidzein and genistein of Kelly to the synergistic beta-conglycinin and apoI of Kohno, Yamada ad Berenbaum(1 and2) because they also lower cholesterol, treat hypercholesterolemia, and one would have the added benefit of treatment of PMS (including PMT) and menopausal symptoms, reduced risk of development of cancer of the prostate, cancer of the breast, cancer of the uterus, cancer of the large bowel, the syndrome in women commonly referred to pre-mentsrual syndrome (PMS), which includes pre-mentsral tension (PMT), many untoward symptoms (including dry vagina, peripheral flushing, depression, etc.) commonly associated in women with menopause and treating benign breast disease in women (benign or cystic disease associated with non-malignant swelling and tenderness of breast tissue)

13. Claims 12, 15, 20, 23, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno, et al., WO 02/26243 A1 (Kohno, et al. EP 1 323 425 A1 - English Equivalent) in view of Yamada, et al, Increased clearance of plasma cholesterol after injection of apolipoprotein E into Watanabe heritable hyperlipidemic rabbits, Proc. Natl. Acad. Sci. USA, January 1989, Vol. 86, pp. 665-669 and further in view of M.C. Berenbaum, Synergy, additivism and antagonism in immunosuppression, A critical review, Clin. Exp. Immunol, 1977, Vol. 28, pp. 1-18 (Berenbaum1) and M.C. Berenbaum, What is Synergy?, Pharmacological Reviews, 1989, Vol. 1969, Vol. 41, pp. 93-141 (Berenbaum2) and further in view of M. Fiordaliso, et al., Dietary Oligofructose Lower

Triglycerides, Phospholipids and Cholesterol in Serum and Very Low Density Lipoproteins of Rats, Lipids, 1995, Vol. 30 No. 2, pp. 163-167.

Kohno, Yamada and Berenbaum(1 and 2) disclose as set forth above. However, none of them teach the additional ingredient of a carbohydrate substantially resistant to digestion, specifically oligofructose.

Fiordaliso discloses that daily administration of a 10% (w/w) oligofructose (a nondigestible oligosaccharide) supplemented containing diet to normolipidemic male rats resulted in a decreased plasma triglycerides, phospholipids and cholesterol. Abstract, pp. 163, 165-167, Tables 1 and 2, Figures 2 and 3. Fiodaliso also discloses that chronic administration of OFS to the rats caused a significant ($P<0.05$) reduction in serum triglycerides and the incorporation of [1-14C] into cellular triglycerides, as a function of incubation time, in heptaocyted isolated from OFS-fed rats was lower than in control cells ($P<0.05$) and after 150 minutes of incubation, the incorporation of [1-14C] palmitate into cellular triglycerides was reduced by 40%. Pp. 165-67, Figures 2 and 3. Fiordaliso further discloses that that the observation that reduced serum triglyceride, phospholipids and cholesterol levels, were mainly due to a decrease in the number of VLDL particles, together with the results of our ex vivo experiments, supports the hypothesis that OFS feeding, like that of other fermentable dietary fibers significantly alters the metabolism of lipids in the liver with, as a likely consequence, a reduction in VLDL production. Pg. 166, Tables 1 and 2, Figures 2 and 3.

Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to have added the preferred carbohydrate substantially resistant to digestion, specifically oligofructose of Fiordaliso to the synergistic beta-conglycinin and apoE of Kohno, Yamada and Berenbaum(1 and2) because it is prima facie obvious as the idea of combining them flows logically

from their having been individually taught in the prior art. See also, MPEP 2144.06 and In re Kerkhoven, cited above. Moreover it would have been obvious to one of ordinary skill in the art at the time of the invention to have added the preferred carbohydrate substantially resistant to digestion, specifically oligofructose of Fiordaliso to the synergistic beta-conglycinin and apoI of Kohno, Yamada ad Berenbaum(1 and2) because it also lowers cholesterol, and one would have the added benefit of lowering triglycerides.

14. Claims 12, 15, 20-22, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno, et al., WO 02/26243 A1 (Kohno, et al. EP 1 323 425 A1 - English Equivalent) in view of Yamada, et al, Increased clearance of plasma cholesterol after injection of apolipoprotein E into Watanabe heritable hyperlipidemic rabbits, Proc. Natl. Acad. Sci. USA, January 1989, Vol. 86, pp. 665-669 and further in view of M.C. Berenbaum, Synergy, additivism and antagonism in immunosuppression, A critical review, Clin. Exp. Immunol, 1977, Vol. 28, pp. 1-18 (Berenbaum1) and M.C. Berenbaum, What is Synergy?, Pharmacological Reviews, 1989, Vol. 1969, Vol. 41, pp. 93-141 (Berenbaum2) and further in view of J. Wojcicki, et al., Clinical Evaluation of Lecithin as a Lipid-lowering Agent, Phytotherapy Research, December 1995, Vol. 9, Iss. 8, pp. 597-599.

Kohno, Yamada and Berenbaum(1 and 2) disclose as set forth above. However, none of them teach the additional ingredient of a phospholipid, specifically lecithin.

Wojcicki discloses that following administration of soybean lecithin (lecithin granulate - Sternpur) for 30 days to patients with hyperlipidaemia mean total cholesterol concentration was significantly decreased by 33%, while LDL-level was diminished by 38%, HDL-cholesterol concentration at the same time was increased significantly by 46% and mean triglyceride concentration was significantly decreased by 33%. Abstract, pp. 597-597, Tables 1-3.

Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to have added the preferred phospholipid specifically lecithin of Wojcicki to the synergistic beta-conglycinin and apoE of Kohno, Yamada and Berenbaum(1 and2) because it is prima facie obvious as the idea of combining them flows logically from their having been individually taught in the prior art. See also, MPEP 2144.06 and In re Kerkhoven, cited above. Moreover it would have been obvious to one of ordinary skill in the art at the time of the invention to have added the preferred phospholipid specifically lecithin of Wojcicki to the synergistic beta-conglycinin and apoI of Kohno, Yamada ad Berenbaum(1 and2) because it also lowers cholesterol, and one would have the added benefit of lowering triglycerides.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER I. HARLE whose telephone number is (571)272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Jennifer I. Harle/

Examiner, Art Unit 1654

Jennifer I. Harle
Primary Examiner
Art Unit 1654

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